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ORIGINAL ARTICLE

Clinical Epidemiological Study of 553 Patients with Chronic Rhinosinusitis in Japan

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ABSTRACT

Background: The relationship between chronic rhinosinusitis (CRS) and asthma has been known for a long time. However, no large studies on the relationship between CRS and lower airway diseases have been reported to date in Japan. Additionally, eosinophilic chronic rhinosinusitis (ECRS) in Japan is considered to be a subgroup of CRS with nasal polyps (CRSwNP) characterized by eosinophil-dominant inflammation. However, the diagnostic criteria of ECRS have not been established.

Methods: To investigate clinical and epidemiological features of patients with CRS from the aspect of their associations with lower airway diseases, 553 patients with CRS who visited one of six local university hospitals were examined and interviewed. Local eosinophilic infiltration was evaluated pathologically by exmining NPs.

Results: The prevalences of olfactory dysfunction (OD) in the patients with nasal polyps (NPs) and those without NPs were 57.0% and 13.7%, respectively ($p < 0.0001$). The prevalence of asthma in all patients was 23.1%. Furthermore, the prevalences of NPs and OD in the patients with asthma and those without asthma were 81.0% and 50.1% ($p < 0.0001$) and 64.2% and 35.7% ($p < 0.0001$), respectively. 97.4% of the patients with asthma had ≥15% mucosal eosinophils, and 87.9% of the patients without asthma had <15% mucosal eosinophilis.

Conclusions: Similar to the relationship between nasal allergy and asthma, CRSwNP may be applicable to the concept of “one airway, one disease”.

KEY WORDS

asthma, chronic rhinosinusitis, eosinophil, nasal polyp, questionnaire survey

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common disease in the otorhinolaryngology field in Japan. Previously, CRS mostly consisted of chronic inflammation caused by occlusion of the sinus ostia. Recently, however, CRS with nasal polyps (NPs), in which distinct eosinophilic infiltration can be observed, is rapidly increasing. This latter disease is called eosinophilic chronic rhinosinusitis (ECRS) in Japan.[1,2] In Europe and the United States, CRS characterized by eosinophilic inflammation is called chronic hyperplastic eosinophilic sinusitis (CHES),[3] eosinophilic mucin rhinosinusitis (EMRS)[4] or chronic hyperplastic rhinosinusitis with nasal polyposis (CHS/NP).[5] Each of these conditions can be considered to be similar to ECRS. Moreover, CRS has recently been divided into two subgroups: chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP).[6] Ishitoya *et al.*[2] reported that the concept of ECRS in Japan would be applicable for CRSwNP in Europe and the United States.

The relationship between CRS and asthma has been known for a long time. However, it is not fully

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understood. An epidemiological study reported that 93% of patients with EMRS were associated with asthma and that 54% of these patients had aspirin-intolerant asthma (AIA).[4] Another study reported that 50% of CHS/NP patients were associated with asthma and that about 30-40% of these patients had AIA.[5] Thus, ECRS is an eosinophilic inflammation that can affect not only the nose and sinuses but also the bronchi, and can be considered to be an airway disease consistent with the concept of "one airway, one disease".

There have been epidemiological studies on upper airway diseases in Japan from the aspect of asthma.[7] However, from the aspect of CRS, no large studies on the relationship between CRS and lower airway diseases have been reported to date. In this study, we conducted a large-scale survey among multiple institutions (six university hospitals). The study focused on the clinical conditions of CRS and assessed the relationships with lower airway diseases.

METHODS

PATIENTS

Patients with CRS who visited one of six local university hospitals during 5 months from June 2005 to October 2005 were evaluated. Patients with CRS who visited during that period were randomly selected, and examined and interviewed for the items described below. A total of 553 patients were included, comprising 317 males, 229 females and 7 patients in whom no gender was specified. The mean age was 51.5 ± 18.8 years (range: 3-92 years) and the mean duration of CRS was 8.8 ± 13.2 years (range: 0.3-66 years).

The study was approved by the ethical committee of each institution, and informed written consent to the study protocol was obtained from all subjects.

CHRONIC RHINOSINUSITIS

The diagnostic criteria for CRS were defined by the clinical symptoms (nasal obstruction, discolored discharge (anterior/posterior nasal drip) or reduction/loss of smell) for more than 12 weeks, plain X-ray imaging and computed tomographic (CT) scanning. The patients were asked about the disease duration, whether they had an olfactory dysfunction (anosmia/hyposmia) and whether they had a history of surgery for sinus diseases. The presence or absence of an olfactory dysfunction was determined based on the patient's complaints. Plain X-ray examination, CT scanning and endoscopy were performed on all patients. The presence or absence of NPs was determined visually using an endoscope. Surgery was reserved for CRS patients with NPs or persistent cases after conservative medication for a few months. Local eosinophilic infiltration was evaluated pathologically using NPs removed during surgery. The NPs were stained with hematoxylin and eosin for detection of tissue eosinophilia. The percentage of eosinophils in each sample was calculated by dividing the number of eosinophils by the total number of inflammatory cells counted. We classified the degree of eosinophilic infiltration into the following three groups by comparing the percentages of eosinophils: mild (<15%); moderate (15-30%) and severe (≥30%). Patients with moderate to severe degrees of eosinophilic infiltration were considered to have the presence of eosinophilic infiltration. Our diagnostic criterion for ECRS is mucosal eosinophilia (≥15%). The procedures were carried out by experienced pathologists without knowledge of the other clinical parameters in each hospital.

LOWER AIRWAY DISEASES

Patients were asked if they had asthma that was still under treatment and about the disease duration. Among the patients with asthma, those who had experienced an attack induced by any non-steroidal anti-inflammatory drug were considered to have aspirin-intolerant asthma (AIA). Patients were also asked whether their asthma had been improved after endoscopic sinus surgery (ESS). Patients whose medication dose or attack frequency had been reduced were categorized into the improved group. The patients were also asked whether they had any chronic obstructive pulmonary diseases (COPD).

STATISTICAL ANALYSIS

The prevalences of NPs and an olfactory dysfunction, prevalences of lower airway diseases, prevalences of NPs and an olfactory dysfunction in patients with each lower airway disease, and surgery rates were evaluated. The chi-square test was used for statistical analyses of differences between groups and values of $p < 0.05$ were considered to indicate statistical significance. JMP software version 7.0.1 (SAS Institute Inc., Cary, NC, USA) was used for all analyses.

RESULTS

NASAL POLYPS AND OLFACTORY DYSFUNCTION IN ALL PATIENTS

Among all the 553 patients with CRS, 309 (55.9%) had NPs and 227 (41.0%) did not have NPs, while no findings were specified for 17 (3.1%). Furthermore, among the 553 patients with CRS, 210 (38.0%) had an olfactory dysfunction and 279 (50.5%) did not have an olfactory dysfunction, while no findings were specified for 64 (11.5%) (Table 1).

The relationship between NPs and olfactory dysfunction was also evaluated. An olfactory dysfunction was present in 176 of 309 (57.0%) patients with NPs, compared with 31 of 227 (13.7%) patients without NPs (Fig. 1). There was a significant difference in the prevalences of olfactory dysfunction between the two groups ($p < 0.0001$).

Table 1 Nasal polyps and olfactory dysfunction in 553 patients with chronic rhinosinusitis

	Present (%)	Absent (%)	Unknown (%)
Nasal polyps	309 (55.9)	227 (41.0)	17 (3.1)
Olfactory dysfunction	210 (38.0)	279 (50.5)	64 (11.5)

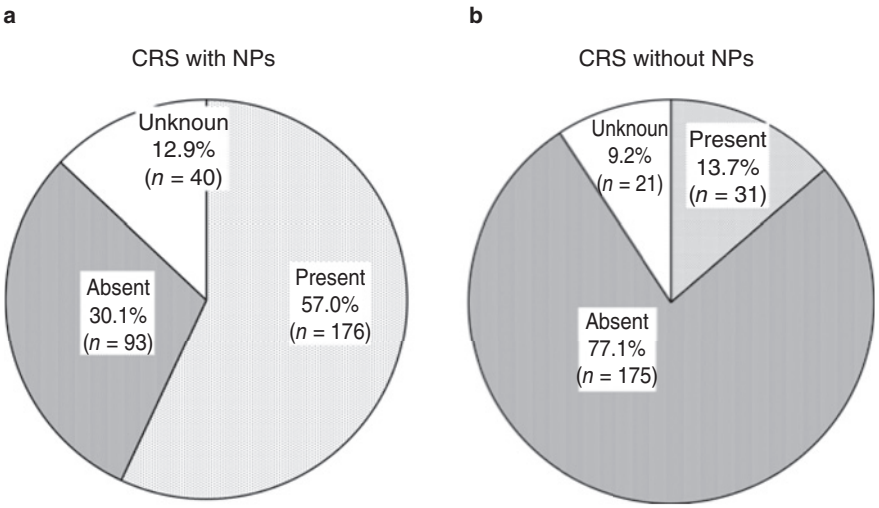

Fig. 1 Relationship between NPs and olfactory dysfunction. An olfactory dysfunction was reported in 176 of 309 (57.0%) patients with NPs (**a**), compared with 31 of 227 (13.7%) patients without NPs (**b**).

Table 2 Nasal polyps and olfactory dysfunction in 255 patients undergoing surgery

	Present (%)	Absent (%)	Unknown (%)
Nasal polyps	172 (67.5)	76 (29.8)	7 (2.7)
Olfactory dysfunction	121 (47.5)	117 (45.9)	17 (6.6)

NASAL POLYPS AND OLFACTORY DYSFUNCTION IN PATIENTS UNDERGOING SURGERY

Among the 553 patients with CRS, ESS was performed in 255 (46.1%). Among the 255 patients who underwent ESS, 172 (67.5%) had NPs and 76 (29.8%) did not have NPs, while no findings were specified for 7 (2.7%). Furthermore, among the 255 patients, 121 (47.5%) had an olfactory dysfunction and 117 (45.9%) did not have an olfactory dysfunction, while no findings were specified for 17 (6.6%) (Table 2).

PREVALENCES OF LOWER AIRWAY DISEASES IN ALL PATIENTS

Among the 553 patients with CRS, 128 (23.1%) had asthma (ATA in 99 [17.9%] and AIA in 29 [5.2%]) (Fig. 2). In addition, 15 patients had COPD (2.7%). The onset times of CRS and asthma were assessed. Among the 128 patients who had both CRS and asthma, the onset times of both diseases could be identified in 52 patients. Of these 52 patients, 15 (28.8%) developed CRS first, 23 (44.2%) developed asthma first and 14 (26.9%) developed both diseases simultaneously. There were no significant differences in the onset times between the two diseases.

PREVALENCES OF NASAL POLYPS AND OLFACTORY DYSFUNCTION IN PATIENTS WITH LOWER AIRWAY DISEASES

The prevalence of NPs was assessed for each lower airway disease. Overall, 76 of 97 (78.4%) patients with ATA, 26 of 29 (89.7%) patients with AIA and 7 of 13 (53.8%) patients with COPD had NPs. Among 400 patients without lower airway diseases, 200 (50.0%) had NPs. As expected, about 90% of patients in the AIA group and about 80% of patients in the ATA group had NPs. The prevalences were significantly higher in the ATA and AIA groups than in the group without lower airway diseases ($p < 0.0001$ for each group) (Fig. 3).

In the same way, the prevalence of patients with an olfactory dysfunction was assessed for each lower airway disease. Overall, 54 of 93 (58.1%) patients with

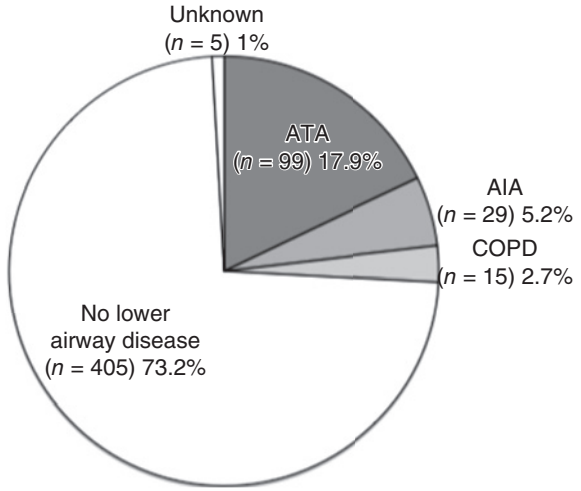

Fig. 2 Prevalences of lower airway diseases in 553 patients with chronic sinusitis. Among the 553 patients, 128 (23.1%) patients were associated with asthma, comprising 99 (17.9%) patients with ATA and 29 (5.2%) patients with AIA.

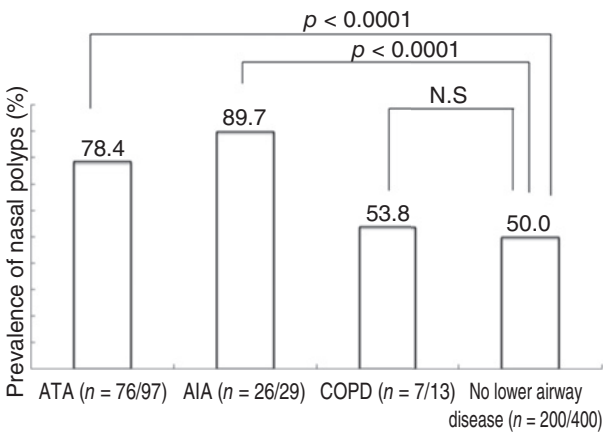

Fig. 3 Prevalences of NPs in patients with lower airway diseases. The prevalences of NPs are significantly higher in the ATA and AIA groups than in the group without lower airway diseases ($p < 0.0001$ for each group). N.S, not statistically.

ATA, 23 of 27 (85.2%) patients with AIA and 9 of 14 (64.3%) patients with COPD had an olfactory dysfunction. Among 359 patients without lower airway diseases, 124 (34.5%) patients had an olfactory dysfunction. The prevalences of patients with an olfactory dysfunction were significantly higher in the ATA and AIA groups than in the group without lower airway diseases ($p = 0.0002$ and $p < 0.0001$, respectively). In addition, the prevalence was significantly higher in the COPD group than in the group without lower airway diseases ($p = 0.0311$) (Fig. 4).

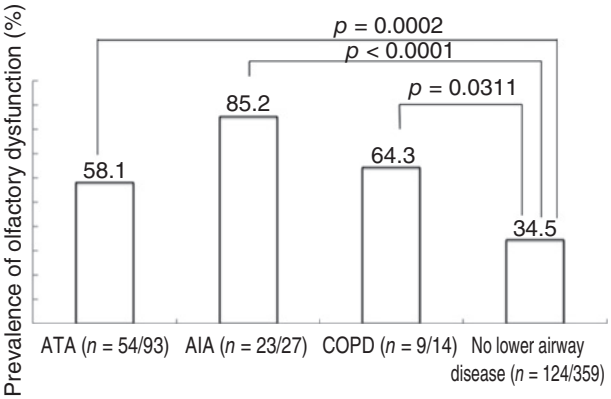

Fig. 4 Prevalences of olfactory dysfunction in patients with lower airway diseases. The prevalences of olfactory dysfunction are significantly higher in the ATA, AIA and COPD groups than in the group without lower airway diseases ($p = 0.0002$, $p < 0.0001$ and $p = 0.0311$, respectively).

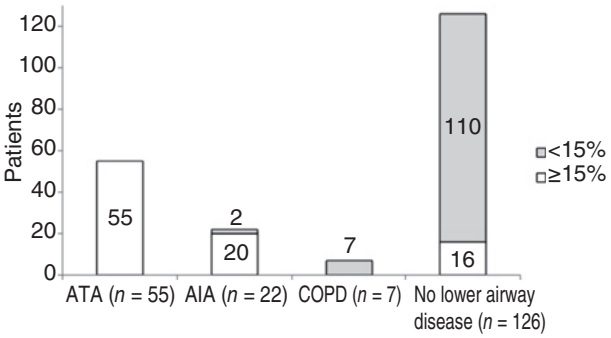

Fig. 5 Eosinophilic infiltration in patients with lower airway diseases. Among 210 patients who assessed for eosinophilic infiltration, 55 of 55 (100%) patients with ATA, 20 of 22 (90.9%) patients with AIA and 16 of 133 (12.0%) patients without asthma had ≥15% eosinophils.

EOSINOPHILIC INFILTRATION

Among 255 patients who underwent ESS, 91 (35.7%) had ≥15% eosinophils and 119 (46.7%) had <15% eosinophils, while no findings were specified for 45 (17.6%). Among 210 patients who assessed for eosinophilic infiltration, 55 of 55 (100%) patients with ATA, 20 of 22 (90.9%) patients with AIA and 16 of 133 (12.0%) patients without asthma had ≥15% eosinophils (Fig. 5).

In addition, among 198 patients in whom the presence or absence of olfactory dysfunction and eosinophilic infiltration could be determined, the relationship between olfactory dysfunction and eosinophilic infiltration was assessed. Among the 198 patients, 99 (50.0%) had an olfactory dysfunction, 90 (45.5%) had eosinophilic infiltration and 71 (35.9%) had both an olfactory dysfunction and eosinophilic infiltration (Table 3).

Table 3 Relationship between olfactory dysfunction and eosinophilic infiltration in 198 patients in whom the presence or absence of an olfactory dysfunction and eosinophilic infiltration could be confirmed

		Olfactory dysfunction	
		+	-
Eosinophilic infiltration (≥15%)	+	71	19
	-	28	80

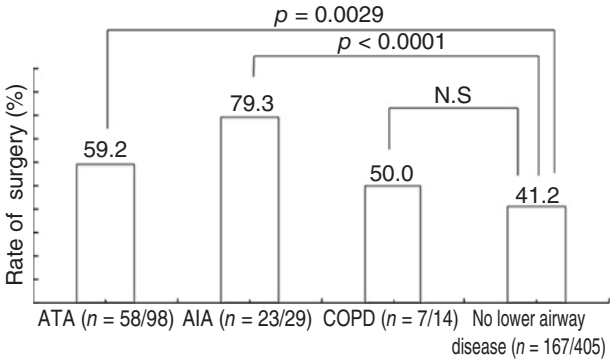

Fig. 6 Surgery rates in patients with lower airway diseases. The rates of surgery are significantly higher in the ATA and AIA groups than in the group without lower airway diseases (p = 0.0029 and p < 0.0001, respectively). N.S, not statistically.

SURGERY RATES IN PATIENTS WITH LOWER AIRWAY DISEASES

Overall, 58 of 98 (59.2%) patients with ATA, 23 of 29 (79.3%) patients with AIA and 7 of 14 (50.0%) patients with COPD underwent ESS. In contrast, among 405 patients without lower airway diseases, 167 (41.2%) underwent ESS. The percentages of patients undergoing ESS were significantly higher in the ATA and AIA groups than in the group without lower airway diseases (p = 0.0029 and p < 0.0001, respectively) (Fig. 6).

IMPROVEMENT IN ASTHMA AFTER SURGERY

Sixty-four patients with asthma in whom changes in asthma after surgery could be identified were evaluated. Among these 64 patients, 47 (73.4%) showed an improvement and 17 (26.6%) did not show any improvement. No patients showed exacerbation of asthma.

DISCUSSION

CRS is a common disease in the otorhinolaryngology field. In recent years, with a decrease in CRS caused by occlusion of the sinus ostia, which previously accounted for the majority of sinusitis cases, sinusitis showing distinct infiltration of activated eosinophils in the sinus mucosa has been increasing. In 2006, CRS has been divided into two subgroups: CRSwNP and CRSsNP.[6] ECRS in Japan is considered to be a subgroup of CRSwNP in Europe and the United States.[2] ECRS is characterized by adult onset, bilateral lesions affecting the ethmoidal sinus rather than the maxillary sinus, frequent olfactory disturbance and resistance to treatment. Given the fact that systemic steroid administration is effective, involvement of allergy is suspected, although it remains unclear whether a type I allergy is involved. Long-term low-dose macrolide therapy is reported to be useful in postoperative treatment for CRS[8] and is widely used in clinical practice. However, in cases involving eosinophilic inflammation, therapies with 14-membered ring macrolide antibiotics are not effective and exacerbation is frequently observed. In addition, it has been reported that the exacerbation may be related to the lower airways, and that it has a high complication rate for asthma including AIA.[4,5]

Because awareness of the association between allergic rhinitis as an upper airway disease and asthma has been growing, international guidelines for allergic rhinitis, designated Allergic Rhinitis and its Impact on Asthma (ARIA), were proposed through a joint project by the WHO and the International Association of Allergy and Clinical Immunology in 2001 and revised in 2008.[9,10] In consideration of the relationship between CRS and asthma, we wondered whether this relationship was consistent with the concept of "one airway, one disease", similar to the relationship between allergic rhinitis and asthma. The prevalences of asthma in patients with CRS in previous reports were 23-50%.[11-13] In this study, 23% of patients with CRS were associated with asthma. These figures are higher than the asthma prevalence of 5% in the general population.[14] In addition, the prevalence of asthma in patients with CRS caused by occlusion of the sinus ostia is considered to comprise only a small percentage.[15] From an epidemiological viewpoint, it indicated that CRS have a relationship with asthma. Moreover, the prevalence of NPs in patients with asthma was significantly higher than that in patients without asthma, indicating that CRSwNP have a close relationship with asthma.

Focusing on eosinophils, Jankowski *et al.*[16] studied nasal polyposis histologically and reported that 102 of 123 (82.9%) patients with nasal polyposis showed >20% eosinophils and all 25 patients in a control group for CRS showed <10% eosinophils. In Japan, histopathological diagnostic criteria for ECRS have not been established. When we defined ≥15% eosinophils as the criterion for ECRS, almost all CRS patients with asthma met our criterion. In addition, 91 (35.7%) of 255 patients who underwent ESS also met our criterion. From histological viewpoint, it is suggested that eosinophilic infiltration are highly correlated with CRSwNP and asthma. Therefore, the concepts of

CRSwNP and CRSsNP need to be separated.

Olfactory dysfunction is one of only four signs and symptoms included in the diagnostic criteria for CRS, and it affects about 60% of CRS patients.[17] Classically, olfactory dysfunction in CRS was caused by mechanical obstruction of the olfactory cleft by physical obstruction of the nasal airways, nasal polyposis, edema, and secretions.[18] However, Kern reported that CRS patients had evidence of direct inflammation of the neuroepithelium and that the degree of inflammatory changes in the neuroepithelium was related to the severity of olfactory dysfunction.[19] In the present study, the prevalences of NPs and olfactory dysfunction were significantly higher in asthmatic groups than in the group without asthma. It seems that olfactory dysfunction by CRS is caused by both conductive and sensorineural process, and that the inflammatory response and the effect to the respiratory epithelium are more severe in CRS patients with asthma than in the patients without asthma.

Interestingly, surgery for CRS improved the asthma symptoms. There are several previous papers reporting that ESS in patients with asthma resulted in improvement of asthma symptoms, reduction in medication doses and less frequent attacks.[20-23] This study was based on a questionnaire survey rather than physical exam, however, 73.4% of patients showed improvement in asthma after ESS, which strongly suggests a relationship between the two diseases in terms of treatment.

Based on the results of this study, the relationship between ECRS and asthma may be applicable to the concept of "one airway, one disease".

CONFLICT OF INTEREST

No potential conflict of interest was disclosed.

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